REMARKS

Status of Claims

Claims 31, 32, 36 and 37 are pending and under consideration on the merits. Claims 1-30, 33, 34 and 35 stand cancelled.

Amendments to the Claims

By this Amendment, claim 34 is cancelled without prejudice against its reintroduction into this or one or more timely filed continuation, divisional or continuation-in-part applications.

Claim 31 is amended to recite "a method of inhibiting the growth of a cancer cell that overexpresses a Dvl-3 protein, the method comprising contacting the cell with a small interfering RNA (siRNA) complementary to all or a portion of a messenger RNA encoding said Dvl-3 protein, wherein said contacting is effective to reduce growth of the cancer cell."

Support for these amendments is found throughout the specification, such as, for example, on page 4, line 18; page 18, lines 5-9; page 49, lines 5-17 and Figure 9.

No new matter is added by virtue of these amendments; entry thereof by the Examiner is therefore respectfully requested.

Interview Summary

Applicants wish to express their gratitude to Examiner Bristol and Examiner Blanchard for the in-person interview conducted with Carol Francis on July 14, 2008. This written summary is submitted in accordance with MPEP §713.04. During the interview the outstanding rejections of the claims under 35 U.S.C. §§102 and 103 were discussed. Amended claims to incorporate the limitations of claim 34 into claim 31 were proposed, which amendments the Examiners indicated should serve to avoid these art-based rejections.

The enablement rejection under §112, ¶1 was also discussed. Applicants' representative discussed generally the rebuttal evidence to be submitted with the response.

The §102(e) rejection based on Alsobrook which had been previously withdrawn was also discussed. The Examiners and Applicants' representative reviewed the withdrawal of the rejection based on the analysis of the lack of an enabling disclosure in the Alsobrook priority documents that provided the basis for an effective date assertedly earlier than the priority date to which Applicants'

claims are entitled. The Examiners confirmed that this analysis was sufficient basis for the withdrawal of the rejection. Applicants' representative also discussed with the Examiner the §1.131 declaration and the relevant dates and evidence.

Withdrawal of Rejections

Applicants acknowledge the Examiner's withdrawal of the rejections made under 35 U.S.C. § 102(b) of claims 31 and 37 by Song et al. based on Applicants' comments at pp. 5-6 of the Response filed November 1, 2007 inasmuch as Song et al. does not teach that dvl-3 is overexpressed in a cancer cell. For at least this reason it is submitted that the claims are novel over the disclosure of Song et al.

Applicants also acknowledge the Examiner's withdrawal of the rejections made under 35 U.S.C. § 102(e) of claims 31, 32, 34 and 37 by Alsobrook et al. (US20030229016; published December 11, 2003; priority to August 26, 2002 and earlier for certain matters) because "the '903 provisional of Alsorook is not enabling for showing inhibition (e.g., antisense (siRNA)) of dvl-3 protein expression in a dvl-3 overexpressing cancer cell," and because the Examiner has concluded that December 2, 2002 was not an enabling date "for the use of siRNA in a method for modulating dvl-3 expression" as the '928 provisional of Alsobrook "does not specifically show that siRNA would work in a dvl-3-overexpressing cancer cell" (Office Action mailed January 17, 2008 at pp. 2-3). For these reasons, it is submitted that the pending claims are novel over the art.

Rejections Under 35 U.S.C. § 103(a)

1. Claims 31 and 37 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over Song et al. (*J. Biol. Chem.* 275:23790-23797 (2000); cited in the PTO 892 form of 5/1/07) in view of Bui et al. (*Biochem. Biophys. Res. Comm.* 239:510-516 (1997)). Office Action page 5, Item 8.

2. Claims 31 and 32 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over Song in view of Bui, and further in view of Engelmann et al. (*Phytomedicine* 9(6):489-495 (2002) Abstract; cited in the PTO 892 form of 5/1/07). Office Action page 12, Item 10.

3. Claims 31 and 36 were rejected under 35 U.S.C. 103(a) as allegedly obvious over Song in view of Bui, and further in view of You et al. (*Proc. Am. Assoc. Cancer Res.* 42: 609 (2001); cited in the

PTO 892 form of 5/1/07) as evidenced by Uematsu et al. (*Oncogene* 22:7218-7221 (2003); cited in the PTO 892 form of 5/1/07). Office Action page 14, Item 11.

The rejections are respectfully traversed for at least the following reasons.

Rejection of claims 31 and 37 over Song and Bui under §103(a)

In order to meet its burden in establishing a rejection under 35 U.S.C. §103(a), the Office must first demonstrate that a prior art reference, or references when combined, teach or suggest all claim elements.[1] Moreover, "[a]ll words in a claim must be considered in judging the patentability of that claim against the prior art."[2]

The Office's interpretation of Song is set out in the Office Action mailed May 1, 2007 at page 5, item 10. There, the Office stated that the reference "teaches that apigenin reduces the levels of Dvl-3 protein in breast cells (Figure 6)…," and "[b]ecause the claims are not limited to the inhibition of Dvl-3 expression directly resulting in the inhibition of cancer cell growth, Song reads on and therefore anticipates the claims."

Here, as amended, independent claim 31 recites "a method of inhibiting the growth of a cancer cell that overexpresses a Dvl-3 protein, the method comprising contacting the cell with a small interfering RNA (siRNA) complementary to all or a portion of a messenger RNA encoding said Dvl-3 protein, wherein said contacting is effective to inhibit growth of the cancer cell." Neither Song nor Bui teach the use of siRNA to inhibit growth of a cancer cell. Accordingly, the combination of references fails to teach all the claim limitations. Therefore, withdrawal of the rejection under 35 U.S.C. § 103(a) is appropriate and respectfully requested.

Rejection of claims 31 and 37 over Song, Bui and Engelmann under §103(a)

The disclosures of Song and Bui upon which the Office relies are discussed above. Engelmann does not remedy the deficiencies of Song and Bui with respect to the amended claims. Engelmann allegedly discloses inhibiting lung cancer growth *in vivo* with apigenin (Office Action mailed January 17, 2008 at page 13, para. 3). Because none of the cited art teaches the use of siRNA to inhibit growth

[1] *See, e.g., In re Royka*, 490 F.2d 981, 985 (CCPA 1974); *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007); *Pharmastem Therapeutics v. Viacell et al.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007); MPEP § 2143(A)(1).
[2] *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

of a cancer cell, the combination of references fails to teach all the claim limitations. Therefore, withdrawal of the rejection under 35 U.S.C. § 103(a) is appropriate and respectfully requested.

Rejection of claims 31 and 37 over Song, Bui, You, and Uematsu under §103(a)

As stated above, neither Song nor Bui teaches the use of siRNA to inhibit growth of a cancer cell. siRNA is not mentioned in the You et al. reference; accordingly, together Song, Bui and You fail to teach all the claim limitations.

With respect to Uematsu et al. (2003), the reference became publically available as of October 16, 2003. The parent provisional application 60/491,350, filed July 31, 2003 discloses use of anti-Dvl-3 siRNA to inhibit Dvl-3 expression in an overexpressing cancer cell. Thus, the Uematsu et al. reference is not available as prior art under 35 U.S.C. § 102(a). It therefore cannot form the basis for a rejection under 35 U.S.C. § 103(a).[3]

Accordingly, for at least the reasons set out above, withdrawal of the rejections under 35 U.S.C. § 103(a) is respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph, enablement

The Office rejects claims 31, 32, 34, 36 and 37 for lack of an enabling disclosure, stating that while the specification is "enabling for inhibiting growth of human mesothelioma cancer cell lines and a human squamous epithelial lung cancer cell line *in vitro* with wnt or dvl-3 siRNA," the specification "does not reasonably provide enablement for using wnt or dvl-3 siRNA to inhibit dvl-3 expression in just any cancer in order to inhibit cancer cell growth much less *in vivo*," (Office Action mailed January 17, 2008 at page 7, para. 9).

Thus, as Applicants understand it, the rejection is based on the assertion that the specification does not provide enablement for:

(1) use of wnt or dvl-3 siRNA to inhibit dvl-3 expression in *any* cancer; and

(2) treating a cell *in vivo* in a mammal with a dvl-3 siRNA (*e.g.*, Office Action, pages 7-8).

[3] *See* MPEP § 715.01 para. 3.

Inhibiting dvl-3 expression in any cancer

Claim 31 does not specify reduction of growth of "just any cancer." Rather, the target cancer cell is one that "overexpresses a Dvl-3 protein." Claim 32, 36 and 37 specify that the cancer cell is a lung cancer cell, a mesothelioma cell, and a breast cancer cell respectively. Accordingly, rejection of the claims based on lack of enablement on this basis is respectfully requested.

Treating a cell in vivo in a mammal

The Office asserts that the art at the time of filing indicated that the use of antisense oligonucleotide therapeutics were highly unpredictable (Office Action mailed January 17, 2008 at page 9) and that based on an article published in *Pharmacology and Therapeutics* eight (8) years ago, the unpredictability stemmed mainly from "'irrelevant cleavage' as a result of the low stringency requirements for RNAse H activity..." *Id.*

Legal Standard for Enablement

The test of enablement is "whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."[4] The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation.[5] Practitioners in the chemical and molecular biology arts frequently engage in **extensive modification of reaction conditions and complex and lengthy experimentation where many factors must be varied to succeed in performing an experiment or in producing a desired result**. The Federal Circuit has found that such extensive experimentation is not undue in the molecular biology arts. For example, in *Hybritech v. Monoclonal Antibodies, Inc.*[6] the court concluded that extensive screening experiments, while being voluminous, were not undue in view of the art which routinely performs such long experiments.

Moreover, a patent need not teach, and preferably omits, what is well known in the art.[7] A considerable amount of experimentation is permissible if it is routine, or if the specification provides a

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[4] *United States v. Telectronics, Inc.*, 8 USPQ 2d 1217, 1233 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). *See also, Genentech, Inc. v. Novo Nordisk*, 42 USPQ 2d 1001 (Fed. Cir. 1997), *cert. denied*, 522 U.S. 963 (1997); *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 USPQ 2d 1001 (Fed. Cir. 1991).

[5] *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985). *See also*, MPEP §2164.01.

[6] 231 USPQ 81 (Fed. Cir. 1986).

[7] *See In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *see also* M.P.E.P. § 2164.01.

reasonable amount of guidance with respect to the direction in which experimentation should proceed.[8] The fact that the required experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation.[9] The scope of enablement must bear only a "reasonable correlation" to the scope of the claims.[10] Applicants "are not required to disclose every species encompassed by their claims" even in an unpredictable art to satisfy the enablement requirement.[11]

Thus, in determining the scope of enablement, the Patent Office must consider the state of the art, including the knowledge available to the skilled artisan:

> The scope of enablement . . . is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill in the art without undue experimentation.[12]

Enablement in Applicants' Specification is Commensurate with the Scope of the Claims

The attached exemplary articles by Sui et al., 2002 (Exhibit A) and Yu et al., 2002 (Exhibit B) indicate that gene expression by way of RNA interference was not unpredictable in the art at the time of filing. For example, Sui et al. report that "[i]n each and every case, we find that these small RNAs efficiently and specifically inhibit the synthesis of proteins encoded by the corresponding genes," (p. 5515 para 4). With respect to the "irrelevant cleavage" noted by the Office, the field had begun to address such as of the filing date. Yu et al. state that transfection of shorter, 21-nt siRNA duplexes into mammalian cells effectively inhibited endogenous genes in a sequence-specific manner, and that these duplexes were short enough so as not to trigger nonspecific dsRNA responses (p. 6047 para. 2). It is submitted that a single article published in *Pharmacology and Therapeutics* eight (8) years ago cannot accurately reflect the overall state of the art at the time of filing. The Stein article, to which the Office refers, cannot support the blanket statement that the entire field of antisense oligonucleotide therapeutics was "highly unpredictable" at the time of the invention. (Office Action mailed January 17, 2008 at page 9).

Further, when the specification and working examples are properly viewed, they provide ample guidance to the ordinarily skilled artisan as to the design of siRNA molecules targeted to various regions

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[8] *See Ex parte Forman*, 230 USPQ 546, 547 (BPAI 1986); *see also In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).
[9] *See In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).
[10] *See* M.P.E.P. § 2164.08; *see, e.g., In re Angstadt*, 537 F.2d 498, 190 USPQ 214 (CCPA 1976).
[11] *See id.* at 503; *see also Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 70 USPQ2d 1321 (Fed. Cir. 2004) *citing AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003) ("That is not to say that the specification itself must necessarily describe how to make and use every possible variant of the claimed invention, for the artisan's knowledge of the prior art and routine experimentation can often fill gaps, interpolate between embodiments, and perhaps even extrapolate beyond the disclosed embodiments, depending upon the predictability of the art.").

of a Dvl-3 gene to inhibit production of the protein *in vitro* and *in vivo*. Applicants' specification provides a working example (*e.g.*, Example 11; page 49, lines 5-17) of an antisense oligonucleotide targeted to the processed Dvl-3 transcript. The Specification provides ample guidance and direction as to how experimentation should proceed for identifying siRNA molecules capable of inhibiting production of Dvl-3. Further, the Dvl-3 gene sequence was available to the skilled artisan at the priority date of the instant application.[13] Thus, it is reasonable to conclude that one skilled in the art at the time of filing could have readily extrapolated the working examples provided in the specification across the entire scope of the claims without excessive and undue experimentation.

Antisense oligonucleotides have since been shown to inhibit expression of their targets *in vivo* (*see* Exhibit C: PCT publication WO 2005/013901, published 17 Feb. 2005, for example). WO 2005/013901 shows efficient inhibition of miR-143 in mice using an antisense oligonucleotide complementary to mir-143 (*see* pages 181-187).

In addition to establishment of efficacy in animal models, at the time of filing of the present application, several antisense oligonucleotides were also known to be efficacious in humans and were advancing through clinical trials (see Exhibit D providing clinical trial records for NCT00017251, NCT00048295, NCT00048321, NCT00078234, and NCT00056173). For example, NCT00056173 describes the use of GTI-2040, an antisense oligonucleotide complementary to the R2 component of ribonucleotide reductase (RNR) mRNA, in combination with capecitabine in the treatment of renal cell carcinoma (study started in March 2002). In addition, NCT00048295 describes the use of an antisense inhibitor of ICAM-1 for the treatment of Crohn's disease (study started in May 2002). In addition, NCT00078234 describes use of Genasense®, an antisense oligonucleotide complementary to Bcl-2, in combination with Rituxan® and fludarabine in the treatment of chronic lymphocytic leukemia (study started Fall 2003). Also at the time of filing of the present application, it was known in the art that antisense oligonucleotides could be readily delivered to the liver (Exhibit E: Bartshe et al., *Pharm Res.* 19(5):676-80 (2002)).

Further, the following table sets forth a collection of references describing technologies for administering antisense RNA. The class of delivery system is set out in the far left column. References describing the delivery technology and available prior to or at the time of the priority date of the instant application are provided in the center column. References confirming efficacy of the delivery technology, but published after the filing date of the instant application, are provided in the right hand

[12] *See Invitrogen Corp. v. Clontech Laboratories, Inc.*, 429 F.3d 1052, 77 USPQ2d 1161 (Fed. Cir. 2005).

column. It is well established decisional law that all available evidence of enablement of an application as of its filing date must be considered, whenever that evidence becomes available, including after the filing date.[14]

All Exhibits referred to herein and the references listed in the table below are provided in an accompanying Information Disclosure statement.

Administration technology	References prior to or at the time of the priority date describing administration technology	References post-filing date confirming efficacy of administration technology
Stable nucleic acid lipid particles	Wheeler (1999) *Gene Therapy* 6:271 Tam (2000) *Gene Therapy* 7:1867	Morrissey (2005) *Nat Biotech* 23:1002 Zimmerman (2006) *Nature* 441:111
Cyclodextrin-based nanoparticles	Gonzalez (1999) *Bioconjugate Chem* 10:1068 Pun (2002) *Bioconjugate Chem* 13:630	Hu-Lieskovan (2005) *Cancer Res* 65:8984 Heidel (2007) PNAS 104:5715
Immunoliposomes	Xu (1999) *Human Gene Therapy* 10:2941 Xu (2002) *Mol Cancer Ther* 1:337 Rait (2002) *Mol Med* 8:475	Pirollo (2007) *Cancer Res* 67:2938
Cationic liposomes/ nanoparticles	Zimmer (1999) *Methods* 18:286 Anwer (2000) *Cancer Gene Therapy* 7:1156 Gokhale (2002) *Clin Cancer Res* 8:3611 Hood (2002) *Science* 296:2404.	Sørensen (2003) *JMB* 327:761 Brignole (2003) *Cancer Letters* 197:231
Polyethylene-based nanoparticles	Robaczewska (2001) *Gene Therapy* 8:874 Aigner (2002) *Gene Therapy* 9:1700 Iwai (2002) *BBRC* 291:48 Kircheis (2002) *Cancer Gene Therapy* 9:673	Urban-Klein (2005) *Gene Therapy* 12:461 Geisbert (2006) *J Infect Dis* 193:1650

In particular, Geisbert et al. shows that treatment of guinea pigs with Ebola virus polymerase siRNAs in polyethylenimine polyplexes reduced plasma virema levels; Pirollo et al. shows injection of mice with nanoimmunoliposome anti-Her-2 siRNA complexes and targeting and sensitization of tumor cells to chemotherapeutics; Morrissey et al. shows improved efficacy of siRNA to HBV when administered as a liposome; and Zimmerman et al. shows systemic delivery of siRNAs directed to apolipoprotein B in non-human primates using a liposomal formulation.

In further support of the enablement of the instant claims for their full scope, Applicants direct the Office to the Board of Patent Appeals and Inferences decision in *Ex parte Gleave* (Exhibit F). In *Ex parte Gleave*, the examiner had rejected the relevant claims recited above for lack of enablement as well as for insufficient written description. The Examiner's basis of the enablement rejection is summarized by the Board as follows:

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[13] *See* Specification, page 6, lines 5-9.
[14] *In re Hogan*, 194 USPQ 527,537 (CCPA 1977).

> According to the examiner, the claims are drawn to "antisense oligo[nucleotides] targeted to any transcript of IGFBP-5 as well as methods of treatment using the antisense oligonucleotides] . . . but the specification is "only enabling for antisense oligos of SEQ ID NO:1 targeted to the IGFBP-5 transcripts of [murine] SEQ ID NO:13, and for the use of SEQ ID NOS:2, 3 and 9 in the inhibition of SEQ ID NO:14 *in vitro*, and does not provide guidance on the *in vivo* inhibition of [human] SEQ ID NO:14" (*Id.*). . . According to the examiner, the "clinical application of antisense therapy is a highly unpredictable art due to obstacles that still face antisense therapy" (Answer, page 9). The obstacles enumerated by the examiner are essentially: the identification of an appropriate target in the disease process, the identification of a molecule that can interfere with the disease process; the identification of a molecule that can interfere with the disease process through specific recognition and affinity; the complexity of cellular uptake of oligonucleotides; and physical barriers due to internal structures of target RNAs and associations with cellular proteins. *Id.*, pages 9-10. In addition, the examiner relies on Gerwtiz and Branch as evidence that the "the antisense approach has generated controversy [among those of skill in the art] with regard to mechanism of action, reliability, and ultimate therapeutic utility" (*id.*, page l0), and the sense in the art is that "efforts should be increased . . . to learn how they may be used successfully in the clinic" (*Id.*).[15]

The Board reversed the rejection by the examiner, directly addressing the arguments on unpredictability in the field:

> We have no reason to doubt the examiner's assessment of the state of the art in general, and we think it is fair to say that the field of antisense therapy is indeed recognized as highly unpredictable by those skilled in the art. Nevertheless, appellants point out, and the examiner appears to acknowledge, that appellants have identified the murine and human IGFBP-5s as appropriate targets in treating androgen-dependent cancers like prostate cancer and breast cancer, and that appellants have identified antisense IGFBP-5 molecules that can delay the progression to androgen independence in the Shionogi tumor model (asserted to be useful model of human prostate cancer) and/or inhibit expression of IGFBP-5 in human prostate cancer cell lines.[16]

After weighing the various factors used for assessing sufficiency of enablement, the Board concluded as follows:

> This concrete guidance, in the form of working examples addresses a number of the examiner's specific concerns, and weigh in favor of finding

[15] *See Ex parte Gleave* at pages 15 and 17.
[16] *See id.* at 17 and 18.

> the specification enabling for claims directed to antisense inhibition of IGFBP-5. In any case, ***the examiner has not explained why the specific guidance in the specification would not, at least to some extent, mitigate or counter balance any remaining factors (e.g., the generally unpredictable nature of the field) tending to weigh against the finding of enablement***.[17]

The facts and the basis of the examiner's enablement rejection in *Ex Parte Gleave* parallel those in the instant case.

The Board's decision with respect to enablement in *Ex parte Gleave* is in accord with the Federal Circuit holding relating to the enablement issue raised in *Falkner v. Inglis* (Exhibit G). There, the Federal Circuit addressed Falkner's assertion that Inglis' specification did not enable the claimed poxvirus vaccine since the specification did not provide any working examples of a poxvirus deleted of "essential genes" or a description of essential genes of poxvirus nor provide any specific guidance on construction of the poxvirus vaccine. The Federal Circuit upheld the decision of the Board, which concluded the specification sufficiently enabled the full scope of the claims. The court emphasized: (a) the publication in professional journals of the DNA sequence of the poxvirus genome along with locations of the "essential regions", (b) the high skill of those in the art; and (c) the well known differences between poxvirus and herpesvirus, such that it would have aided a person skilled in the art to apply the lesson of the herpesvirus example to the poxvirus. The court reiterated the Board's observation:

> The mere fact that the experimentation may have been difficult and time consuming does not mandate a conclusion that such experimentation would have been considered to be "undue" in this art.[18]

Applicants point out that a poxvirus is not a single type of virus, but comprises a large family of DNA viruses that replicate in the cytoplasm, and as suggested by Exhibit H (Gubser et al., 2004, "Poxvirus Genomes: A Phylogenetic Analysis," *J. Gen. Virol.* 85:105-117), not all poxviruses had been sequenced by the priority date of the *Inglis* application (Ser. No. 08/1459,040 filed September 25, 1990), and yet the Board of Patent Appeals and Interferences, as confirmed by the Federal Circuit, held the

[17] *See id.* at 18 (emphasis added).
[18] *See Falkner v. Inglis*, 448 F.3d at 1365.

Inglis specification enabled for the full scope of the claims to poxvirus vaccines. A similar outcome is presented in *Invitrogen Corp. v. Clontech Laboratories, Inc.* (Exhibit I).[19]

The claims in the *Invitrogen* case encompassed compositions of a modified reverse transcriptase enzyme lacking RNase activity. The claims encompassed the genus of such modified enzymes, where the unmodified enzyme could be from a variety of organisms, including "retrovirus, yeast, *Neurospora*, *Drosophila*, primates, and rodents."[20] The working example was limited to generation of the modified (*i.e.*, deletion mutant) form based on the enzyme obtained from Maloney Murine Leukemia Virus. Despite the limited disclosure, the Federal Circuit affirmed the lower court's ruling that the specification enabled the full scope of the claims.[21]

Given (1) the state of the art for antisense products, (2) the knowledge that antisense oligonucleotides can reach the target tissue in question, (3) the demonstrations in the art that antisense oligonucleotides can inhibit targets including siRNAs *in vivo*, and (4) the instant disclosure that antisense oligonucleotides can inhibit growth of a cancer cell that overexpresses Dvl-3 protein, the specification provides adequate enablement for one of skill in the art to make and use the claimed invention.

Overall, Applicants note that the presence or absence of working examples is but one factor to be taken into consideration in determining whether the specification is enabling for the full scope of the claims. Under MPEP § 2164.02 the consideration is whether one skilled in the art would be expected to be able to extrapolate the provided examples across the entire scope of the claim. Compliance with the enablement requirement under 35 U.S.C. §112, first paragraph does not require or mandate that a specific example be disclosed. The specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice the invention without undue experimentation.[22] Furthermore, "[n]othing more than objective enablement is required, and therefore it is irrelevant whether [a] teaching is provided through broad terminology or illustrative examples."[23]

In view of the evidence as a whole, and in accord with decisions by the Board of Patent Appeals and Interferences and the Federal Circuit, the present specification sufficiently enables a person of skill in the art to which it pertains to make and use the claimed invention without undue experimentation for

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[19] 429 F.3d 1052, 77 USPQ2d 1161 (Fed. Cir. 2005).
[20] *See id.* at 1071.
[21] *See id.*
[22] *In re Borkowski*, 164 U.S.P.Q. 642, 645 (CCPA 1970).
[23] *In re Robins* 166 U.S.P.Q. 552, 555 (CCPA 1970).

the full scope of the claims. It is submitted that the descriptions in the Specification, including the working examples, counterbalance any general unpredictability in the field of antisense technology that might bear on the claimed subject matter. Based on the disclosure provided in the application, one skilled in the art would be able to extrapolate the working examples to inhibit Dvl-3 signaling in a cell *in vivo*.

Therefore, Applicants submit that the rejection of claims 31, 32, 34, 36 and 37 under 35 U.S.C. §112, first paragraph has been adequately addressed in view of the remarks set forth above. Withdrawal of the rejection is appropriate and respectfully requested.

CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCSF-371.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

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Enclosures:

- **Exhibit A:** Sui et al. 2002, *PNAS* 99(8) 5515-5520.
- **Exhibit B:** Yu et al. 2002, *PNAS* 99(9):6047-6052.
- **Exhibit C:** PCT publication WO 2005/013901; Esau et al., *Cell Metabolism*, 3:87-98 (2006).
- **Exhibit D:** Internet printouts regarding providing clinical trial records for NCT00017251, NCT00048295, NCT00048321, NCT00078234, and NCT00056173.
- **Exhibit E:** Bartshe et al., *Pharm Res.* 19(5):676-80 (2002)
- **Exhibit F:** *Ex Parte Gleave.*
- **Exhibit G:** *Falkner v. Inglis.*
- **Exhibit H:** Gubser et al., 2004, *J. Gen. Virol.* 85:105-117.
- **Exhibit I:** *Invitrogen Corp. v. Clontech Laboratories, Inc.*

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